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Case Report

Pituitary Apoplexy With Transition to Acute Hypophysitis in a Patient With Sars-CoV-2 Pneumonia

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Abstract

COVID-19 is a systemic disease associated with respiratory insufficiency, systemic inflammation, as well as coagulation, neurological, and endocrine disorders. Among them pituitary apoplexy (PA) as well as, more rarely, acute hypophysitis (AH) have been reported. In the present report, we described a case of PA in an 84-year-old man with SARS-CoV-2 pneumonia, with a previous unknown pituitary adenoma and a possible but not confirmed overlap with transitory AH. After reviewing the available literature, we discuss the potential clinical and pathophysiological relationship between PA and AH. Furthermore, we focus on the neuroradiological features of pituitary lesions in the presence of SARS-CoV-2 infection.

Key Words: pituitary, pituitary apoplexy, hypophysitis, COVID-19, SARS-CoV-2 pneumonia

There are multiple plausible mechanisms for pituitary dysfunction following SARS-CoV-2 infection. Expression of angiotensin-converting enzyme 2 receptors promotes entry of SARS-CoV-2 into cells, and proinflammatory cytokines from the infection potentially lead to acute hypophysitis (AH) [1]. However, few data are available on this topic as opposed to what has been described for the thyroid [1]. SARS-CoV-2 can induce coagulopathy and, when combined with anticoagulation therapy, can favor bleeding in the central nervous system or pituitary [1].

In the present report, we describe a case of a pituitary apoplexy (PA) that occurred during SARS-CoV-2 infection in a patient with a preexisting unknown pituitary adenoma, with the possible overlap with transitory AH. After reviewing the available literature, we discuss the potential clinical and pathophysiological relationship between these 2 conditions.

Case Presentation

An 84-year-old Caucasian man was admitted to the emergency department of a tertiary care hospital in Piedmont, Italy, in November 2020, because of a 2-day history of intense frontal headache, photophobia, and vomiting. The patient had been discharged 3 weeks earlier from the same hospital because of SARS-CoV-2 pneumonia that had been treated with low-flow oxygen, dexamethasone, and low-dose enoxaparin for 10 days. After discharge, dexamethasone was tapered down and switched to prednisone 12.5 mg/die orally for 3 days and then stopped. The patient had a medical history of type 2 diabetes mellitus on metformin and linagliptin, coronary artery disease on low-dose aspirin, and arterial hypertension treated with amlodipine. Vital signs on admission revealed 95% oxygen saturation on room air and normal respiratory rate and blood pressure while heart rate had an irregular rhythm. No other signs on physical examination were present. Electrocardiogram showed new-onset atrial fibrillation (AF).

Diagnostic Assessment

On admission, a noncontrast head computed tomography (CT) scan showed a mass in the sellar region that bordered on the optic chiasm, compatible with a pituitary adenoma. This preexisting condition was unknown, and there were no signs of bleeding or acute ischemic lesions. Chest CT scan was consistent with late-stage SARS-CoV-2 pneumonia. Laboratory tests revealed neutrophilic leukocytosis, a slight increase in C-reactive protein (CRP) (12.9 μg/L, normal values < 5) and blood glucose while other biochemical tests were within normal limits. Positivity for SARS-CoV-2 RNA was detected. The patient was treated with enoxaparin (6000 IU subcutaneous twice daily) for AF, bisoprolol, analgesics, and antiemetic drugs. He was admitted to the medicine department and on day 1 the headache persisted with the onset of confusion, hypotension, bilateral ptosis, and ophthalmoplegia with diplopia. An increased white blood cell count as well as a marked increase of CRP (up to 198 μg/L) was found (Table 1). Neurological examination revealed abnormality in the third cranial nerve function whereas fundoscopic evaluation was negative for papilledema or optic atrophy. Due to the rapidly worsening condition, a cerebral gadolinium-based contrast magnetic resonance imaging (MRI) revealed a pituitary mass with signs of bleeding consistent with PA (Fig. 1). The MRI showed an evident "snowman

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Table 1. Laboratory tests on admission and at follow-up

	On admission	Follow-up at 6 months	Normal values
Cortisol (μg/dL)	4.7	13.6	5.30-22.5
ACTH (pg/mL)	11	-	4.7-48
TSH (μIU/mL)	0.152	1.868	0.350-4.500
Free T3 (pg/mL)	1.9	2.3	2.3-4.2
Free T4 (pg/mL)	7.4	15.7	8-17.6
IGF-1 (ng/mL)	9.6	-	61-476
Prolactin (μIU/L)	36.3	128	44.5-375
LH (mIU/mL)	0.3	-	1.5-34.6
GH (ng/mL)	0.10	-	0.0-2.47
Testosterone (ng/mL)	<0.07	1.03	0.86-7.88
Na + (mEql/L)	137	141	132-146
Urine osmolality (mOsm/kg H_2O)	663	-	20-1200
Serum osmolality (mOsm/kg H_2O)	307	-	275-300
CRP (mg/L)	12→198	3.78	0-5
ERS (mm/h)	4	12	0-20

Abbreviations: ACTH, adrenocorticotropin; CRP, C reactive protein; ERS, erytrocite sedimentation rate; GH, growth hormone; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; TSH: thyroid-stimulating hormone.

sign" shape in basal T1 and T2 weighted sequences and a "ring sign" design after injection of the contrast medium. In addition, there was a loss of posterior pituitary T1 high signal intensity [posterior pituitary high intensity (PPHI)] on the sagittal T1 plane sequences and an intense and homogeneous enhancement of the infundibulum, a thickening of the pituitary stalk (6.5 mm), and a dural tail sign, suggesting a PA with possible concomitant radiological signs of AH (Fig. 1). Due to the high preoperative risks, neurosurgeons did not recommend surgery or biopsy. On day 1 multiple pituitary hormone deficiencies were documented with plasma and urine osmolality in the normal range (Table 1).

Treatment

Hydrocortisone at the dosage of 200 mg/day intravenously was given, then switched to intravenous dexamethasone 8 mg/daily. Oral L-thyroxine was started while subcutaneous insulin was administered to control hyperglycaemia.

Outcome and Follow-Up

On day 4 of hospitalization, CRP decreased to 23.7 μg/L and a partial recovery of ptosis and ophthalmoplegia together with headache resolution occurred; a second MRI revealed a reduction in the thickening of the pituitary stalk, infundibulum, and dura mater (Fig. 2).

The patient was discharged after 10 days on oral prednisone treatment to be gradually tapered off over 6 weeks and switched to oral cortisone acetate 25 mg daily, along with subcutaneous insulin L-thyroxine, calcium, and vitamin D. CRP further decreased to normal values (Table 1). One month following discharge, complete recovery of ptosis and visual function were noted, serum free thyroid hormones and cortisol were within normal range on replacement therapy. A further MRI showed a global reduction of the glandular size, a normal infundibulum and pituitary stalk enhancement, and a normal morphology of the cavernous sinuses. On the other hand, absent spontaneous signal hyperintensity in T1 of the neurohypophysis together with a prevalent intraglandular signal cystic fluid with areas of low signal in T2 due to hemosiderin in previous intraglandular bleeding were still present (Fig. 3). Direct oral anticoagulant was started again for permanent AF. A further follow-up at 6 months showed that the patient was in good clinical condition, inflammation markers were still off, thyroid hormones and cortisol levels were normal during replacement therapy, and thyroid-stimulating hormone and prolactin levels reached normal range while hypogonadism was still present.

Discussion

We report a case of PA that occurred during SARS-CoV-2 pneumonia in an elderly patient with an unknown pituitary mass consistent with nonfunctioning adenoma, in whom some neuroradiological findings led to hypothesize a transitory combined AH. This case underlines the close relationship between SARS-CoV-2 infection and pituitary as well as the challenging workup in the differential diagnosis between PA and AH. It is well known that COVID-19 is a systemic disease with a cascade of events leading to multiorgan involvement. PA has been reported among the neurological and endocrinological manifestations of COVID-19 [1]. Generally, PA is a rare condition with a prevalence of 6.2 per 100 000 persons, with symptomatic PA occurring in about 2% to 12% of patients with adenoma [2]. PA is commonly a consequence of intrasellar hemorrhage and/or infarction of the hypophysis, typically in the setting of a preexisting adenoma. Although its exact mechanism is not fully understood, several predisposing factors have been suggested, including coagulopathy and anticoagulants, platelet dysfunction, thrombocytopenia, acute derangements in blood pressure, and greater metabolic demands [2].

In most cases of PA, SARS-CoV-2 infection in patients with preexisting macroadenoma was identified [2, 3]. A case of a nearly full-term gravid patient presenting with PA and acute SARS-CoV-2 infection has also been reported [4]. In our patient, a preexisting pituitary mass was present and some predisposing factors were evident such as the viral infection and the anticoagulation therapy.

On the contrary from PA, very few cases of COVID-19-related AH have been described so far. Leow et al reported postinfectious AH in patients who had survived the previous SARS epidemic: in a series of 61 patients evaluated after recovery from SARS in Singapore, the most frequent endocrine complication was hypocortisolism that in most cases proved to be reversible [5].

A case of AH after SARS-CoV-2 infection was reported in a 27-year-old male patient presenting with vomiting, headache, hyponatremia, hypocortisolism, hypothyroidism, and hypogonadism. MRI revealed a diffusely enlarged pituitary gland and thickened stalk with homogenous postcontrast [6].

The first case of AH in pediatric age has been recently reported in a 18-year-old girl who had a history of symptomatic COVID-19 3 weeks prior to the onset of severe headache [7]. MRI of the brain revealed thickening and enlargement of the

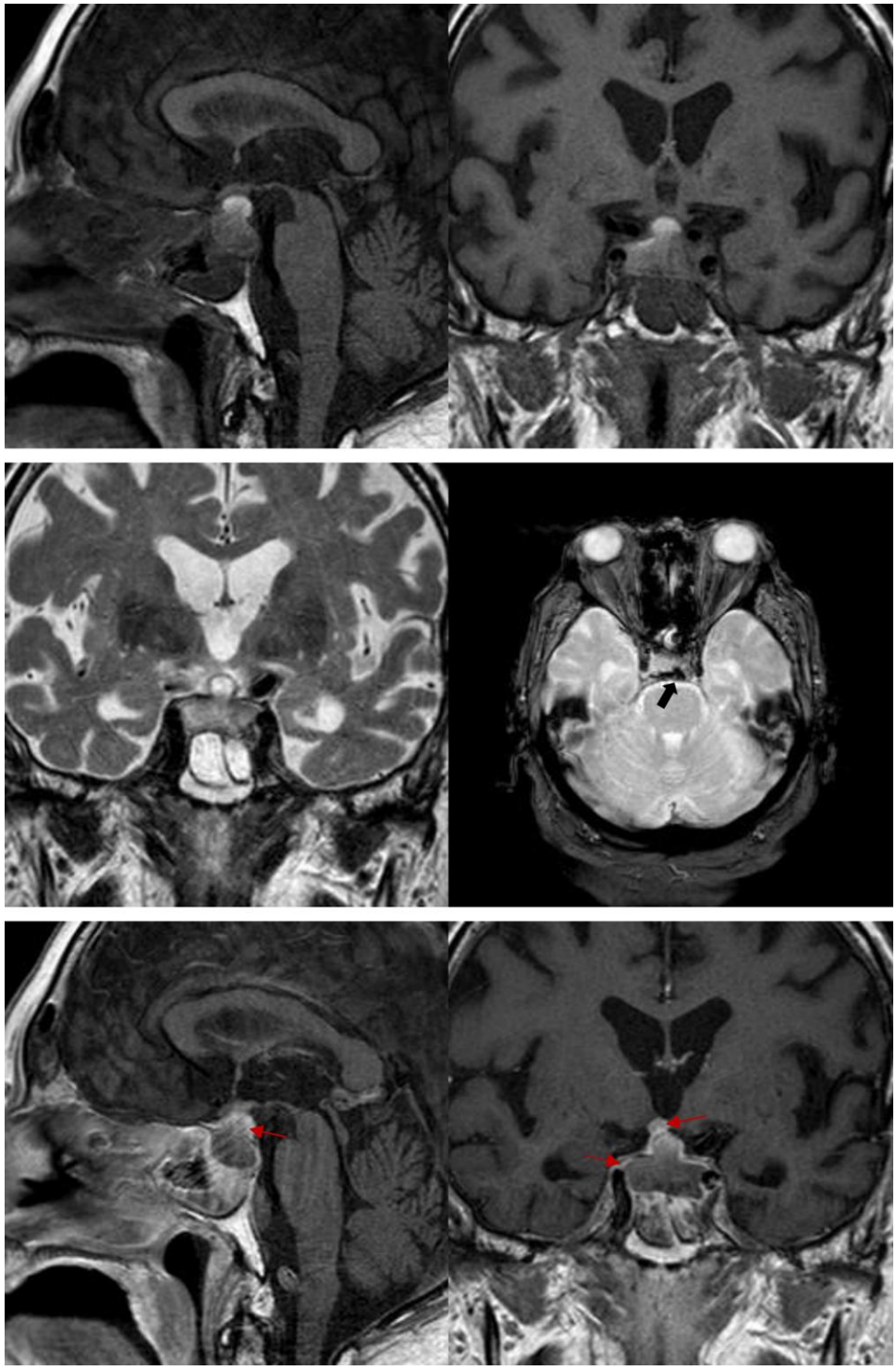

Figure 1. The first magnetic resonance imaging examination confirmed a sellar and suprasellar mass iso-hyperintense to the brain tissue on T1 and T2 weighted images with an hypointense area on T2*Fast Field Echo images as hemosyderin component (black arrow) in possible subacute bleeding. After intravenous injection of gadolinium, an evident ring sign, thickening of the pituitary stalk, and infundibulum and dural tail sign (red arrow) have been detected; an evident sphenoidal mucosal thickening is also present.

infundibulum with homogeneous contrast enhancement of the hypophyseal axis. Based on the suspicion for lymphocytic hypophysitis, she was started on intravenous methylprednisolone, and symptomatic clinical improvement was promptly seen [7]. Misgar et al described a case of infundibuloneurohypophysitis that presented with central diabetes insipidus as a late complication of COVID-19 [8].

With regards to the pathogenetic mechanism linking viral infection and AH, cytokine storm and virus tropism for neural tissue may represent precipitating risk factors [1].

Diagnosis of both PA and AH is based on clinical, laboratory, and imaging data, whereas pituitary biopsy, though rarely indicated, may provide a definitive histological diagnosis [2, 9].

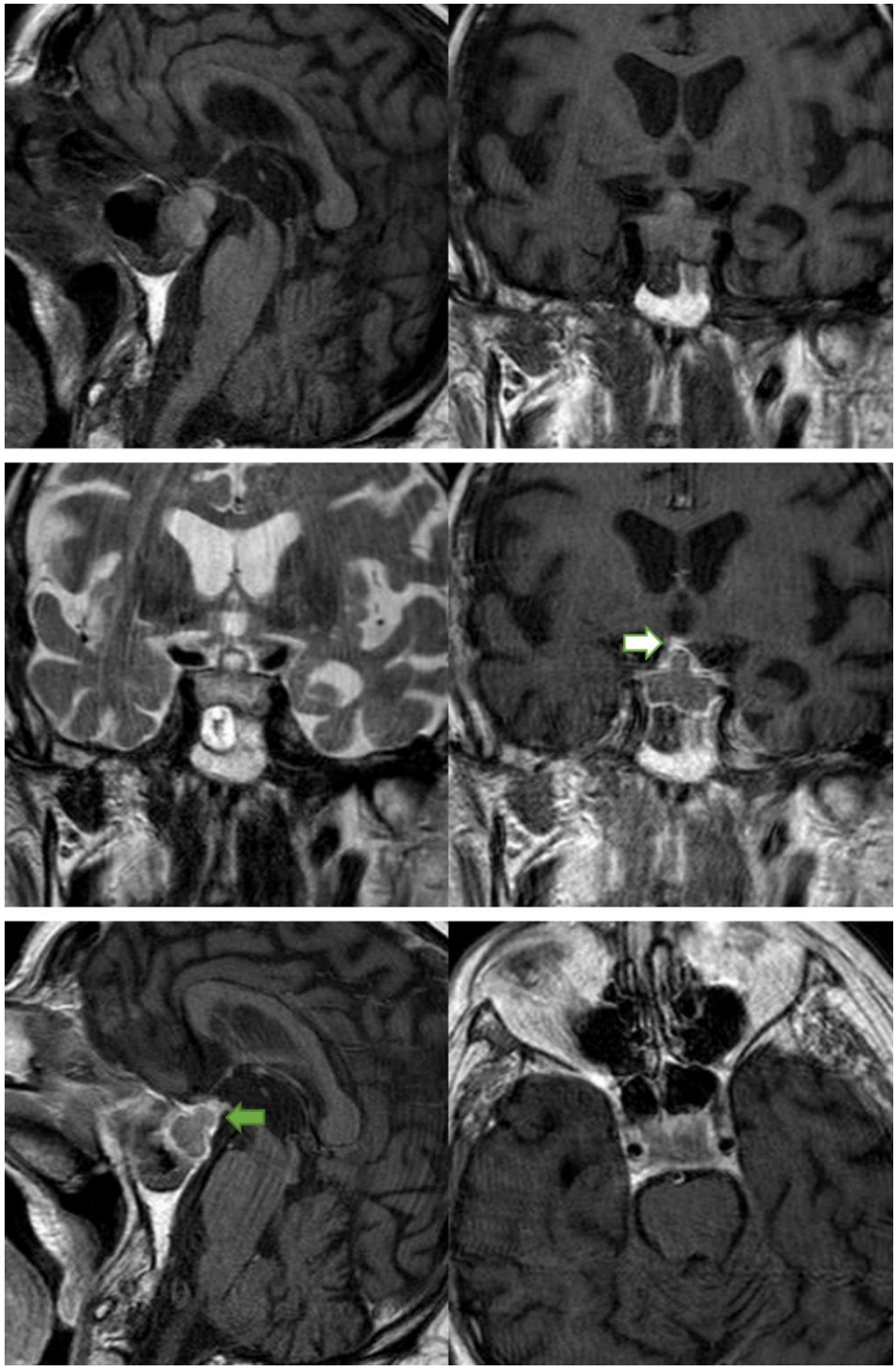

Figure 2. The second magnetic resonance imaging examination revealed a partial improvement with an initial reduction of the thickening of the pituitary stalk (green arrow), infundibulum, and the dura mater; the parasellar T2 dark sign does not appear, and the variation of the intralesional signal in T1 and T2 weighted images is depicted in the basal sequences.

In our case, clinical and biochemical data were in line with the diagnosis of PA, though some findings could not rule out the combination of a transitory AH (the recent viral infection, the increase of inflammatory markers that rapidly decreased together with headache resolution after steroid treatment). Neuroradiological findings were not clearly definitive, and overlapping signs of PA and AH were present. The CT scan at admission documented the presence of a sellar mass, likely due to adenoma, as evidenced by the presence of the "snowman sign" shape associated with widening of the sellar profiles. The basal acquisitions of the first MRI study documented an iso-hyperintense intraglandular signal in T1 and T2 with mass effect on the infundibular region, absence of the representation of spontaneous signal hyperintensity of

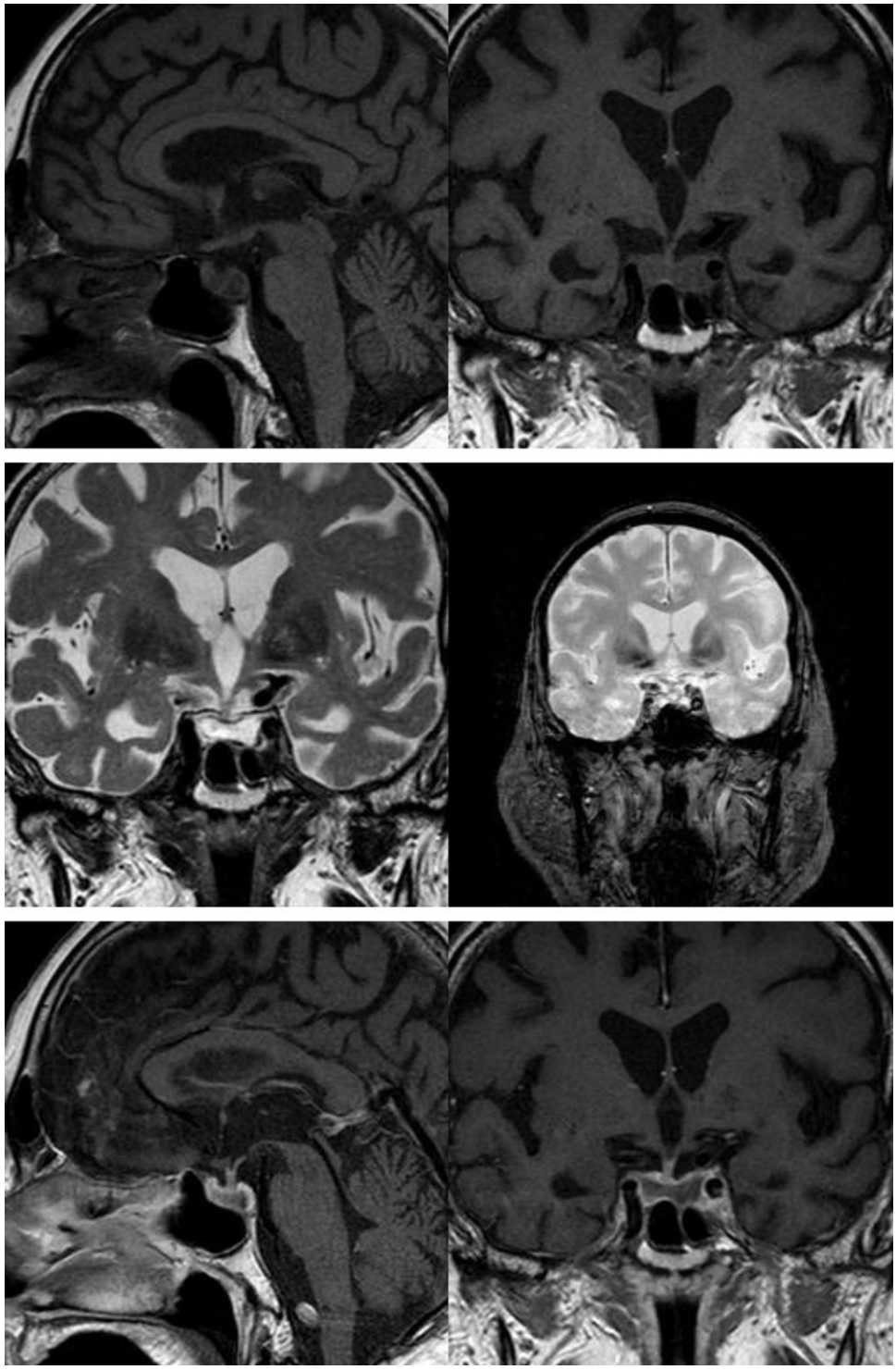

Figure 3. The last magnetic resonance imaging examination reported a morphological pattern that was partially normalized if compared to the first examination. In particular, a global reduction of the glandular size, a normal infundibulum and pituitary stalk enhancement, and a normal morphology of the cavernous sinuses were apparent while the persistence of absent spontaneous signal hyperintensity in T1 of the neurohypophysis together with a prevalent intraglandular signal cystic fluid with areas of low signal in T2* due to hemosiderin in previous intraglandular bleeding (pituitary apoplexy) were still present.

the neurohypophysis in T1, and an evident thickening of the sphenoidal sinus mucosa. After injection of the paramagnetic contrast agent, the presence of the "ring sign" design with peripheral contrast impregnation of the glandular tissue, a thickening of the infundibulum region (about 6.5 mm) and pituitary stalk, and a dural tail sign along the posterosuperior glandular profile became evident. MRI examination suggested PA, in a possible preexisting pituitary adenoma with mass effect and cranial dislocation of the peduncle. However, concomitant findings observed in some cases of lymphocytic hypophysitis such as absent PPHI, dural tail sign, infundibulum, and pituitary stalk thickening were present. On the other

hand, the T2 parasellar dark sign was not present, which, along with PPHI, is very specific to distinguish pituitary adenoma from AH [10]. On MRI performed at 4 weeks after admission, normal pituitary stalk thickness and contrast enhancement were observed, with persistent PPHI absence. At this time, a decrease in the size of the pituitary adenoma was recorded. In particular, a global reduction of the glandular size, a normal infundibulum and pituitary stalk enhancement, and a normal morphology of the cavernous sinuses were apparent together with a prevalent intraglandular cystic signal with areas of low T2 signal due to hemosiderin in previous bleeding. Hence, all together, the clinical, biochemical, and neuroradiological findings contributed to the diagnosis of a PA in a preexisting mass with a suspected transitory associated AH.

Though the diagnostic workup can be challenging, the management of both PA and AH can be similar and includes hormone replacement therapy (if hypopituitarism is present) and control of symptoms with glucocorticoids [2, 9]. In AH, however, glucocorticoids can be used both as anti-inflammatory and immunosuppressive agents, either alone or in combination with other immunosuppressive agents (eg, azathioprine, methotrexate, cyclosporin, rituximab), which have demonstrated variable efficacy in reducing pituitary swelling and restoring pituitary function [9]. In contrast, pituitary surgery is reserved for patients unresponsive to medical therapy and/or who have progressive disease [2, 9].

We recognize that our case has several limitations. First, due to the high surgical risk, we could not perform a biopsy to confirm the suspected diagnosis of coexisting PA and AH. Furthermore, a spinal tap was not done, which could have shown a possible direct invasion of SARS-CoV-2 into the central nervous system.

In addition, we did not check in our patient the presence of primary immunological disorders or measured immunoglobulin G-4 levels in order to rule out a immunoglobulin G-4-related disease, an immune-mediated inflammatory disease rarely involving pituitary and causing hypophysitis [9].

Nevertheless, the strengths of our study are based on the monitored and close clinical, neuroradiological, and biochemical follow-up that led to formulate and discuss this diagnostic hypothesis.

Learning Points

- The pituitary gland should be supervised as a target organ in patients with COVID-19 for the rare development of PA or AH or the even more rare, but nevertheless possible, coexistence of these 2 entities.
- The propensity of SARS-CoV-2 infection to propagate microvascular ischemia and the concomitant use of anticoagulation therapy in COVID-19 can favor the occurrence of bleeding at the pituitary.
- The management of anticoagulant and antiaggregant therapy in patients with pituitary adenoma and SARS-CoV-2 infection requires balancing thrombotic and haemorrhagic risk.
- The neuroradiological description of sellar mass in the presence of SARS-CoV-2 infection can be challenging, and some overlap between apoplexy and hypophysitis can be found.
- Acute pituitary disorders can be challenging as in the case of overlapping conditions such as preexisting unknown pituitary adenoma complicated by an apoplexy in the adenoma and a suspected concurrent acute hypophysitis.

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Author Contributions

Conceptualization, L.G.; methodology, L.G.; writing—original draft preparation, L.G., S.D., N.F., and G.R; writing—review and editing, L.G., S.D., N.F., and G.R.; visualization, N.F. and S.D.; supervision, L.G. All authors have read and agreed to the published version of the manuscript.

Summary

The pituitary gland should be supervised as a target organ in patients with COVID-19 for the rare development of pituitary apoplexy (PA) or acute hypophysitis (AH) or the even more rare, but nevertheless possible, coexistence of these 2 entities.

The neuroradiological description of sellar mass in the presence of SARS-CoV-2 infection can be challenging and some overlap between PA and AH can be found.

Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability

Original data generated and analyzed during this study are included in this published article.

References

1. Frara S, Allora A, Castellino L, di Filippo L, Loli P, Giustina A. COVID-19 and the pituitary. *Pituitary*. 2021;24(3):465-481.
2. Briet C, Salenave S, Bonneville J-F, Laws ER, Chanson P. Pituitary apoplexy. *Endocr Rev*. 2015;36(6):622-645.
3. Martinez-Perez R, Kortz MW, Carroll BW, *et al.* Coronavirus disease 2019 and pituitary apoplexy: a single-center case series and review of the literature. *World Neurosurg*. 2021;152:e678-e687.
4. Chan JL, Gregory KD, Smithson SS, Naqvi M, Mamelak AN. Pituitary apoplexy associated with acute COVID-19 infection and pregnancy. *Pituitary*. 2020;23(6):716-720.

5. Leow MK-S, Kwek DS-K, Ng AW-K, Ong K-C, Kaw GJ-L, Lee LS-U. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). *Clin Endocrinol (Oxf)*. 2005;63(2): 197-202.
6. Nonglait PL, Naik R, Raizada N. Hypophysitis after COVID-19 infection. *Indian J Endocrinol Metab*. 2021;25(3):255-256.
7. Joshi M, Gunawardena S, Goenka A, Ey E, Kumar G. Post COVID-19 lymphocytic hypophysitis: a rare presentation. *Child Neurol Open*. 2022;9:2329048X221103051.
8. Misgar RA, Rasool A, Wani AI, Bashir MI. Central diabetes insipidus (infundibuloneuro hypophysitis): a late complication of COVID-19 infection. *J Endocrinol Invest*. 2021;44(12):2855-2856.
9. Joshi MN, Whitelaw BC, Carroll PV. Mechanisms in endocrinology: hypophysitis: diagnosis and treatment. *Eur J Endocrinol*. 2018;179(3):R151-R163.
10. Agarwal A, Bathla G. Parasellar T2 dark sign on magnetic resonance imaging to differentiate lymphocytic hypophysitis from pituitary adenoma. *Surg Neurol Int*. 2020;11:239.